



The significance of adiponectin as a biomarker in metabolic syndrome and/or coronary artery disease

Značaj adiponektina kao biomarkera metaboličkog sindroma i/ili koronarne bolesti

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Abstract

Background/Aim. Adiponectin exerts profound protective actions during insulin resistance or prediabetes progression towards more severe clinical entities such as metabolic syndrome and/or cardiovascular disease. Since hypoadiponectinemia contributes to the pathophysiology of the metabolic syndrome and coronary artery disease the level of circulating adiponectin may be an early marker of cardiovascular events. The aim of this study was to determine the relationships between serum adiponectin levels and parameters of both insulin sensitivity and obesity in patients with the metabolic syndrome and/or coronary artery disease, as well as to assess predictive value of adiponectin serum levels as a biomarker of these entities. **Methods.** The study included 100 patients with metabolic syndrome and/or coronary artery disease with different degree of insulin resistance and healthy, normoglycemic individuals. The control group comprising healthy, normoglycemic individuals was used for comparison. Serum level of adiponectin, fasting glucose, fasting insulinemia Homeostasis Model Assessment of Insulin Resistance (HOMA-

IR) index and anthropometric parameters were determined in all the subjects. Adiponectin was measured by using the ultrasensitive ELISA method. Insulinemia was measured by the radioimmunoassay (RIA) method. The presence of glycemic disorders was assessed on the basis of oral glucose tolerance test (OGTT). **Results.** Adiponectin level was inversely correlated with age ($\rho = -0.015$), parameters of both obesity ($R = 0.437$; $p < 0.001$) and insulin resistance ($R = 0.374$; $p < 0.01$). Decreasing in the level of adiponectin was strongly implicated in the development of insulin resistance. Most importantly, a statistically significant rapid decrease in adiponectin was in the prediabetic stages ($p < 0.01$). The predictor value of adiponectin was $1,356.32 \pm 402.65$ pg/mL. **Conclusions.** The obtained results suggest that adiponectin may be a useful marker in identification of individuals with risk of developing metabolic syndrome and coronary artery disease, as well as a predictor of prediabetes.

Key words:
adiponectin; biological markers; metabolic syndrome x;
coronary disease.

Apstrakt

Uvod/Cilj. Adiponektin ispoljava snažno zaštitno dejstvo u toku progresije insulinske rezistencije ili predijabetesa u ozbiljnije kliničke entitete, kao što su metabolički sindrom i/ili kardiovaskularne bolesti. Pošto hipoadiponektinemija doprinosi patofiziologiji metaboličkog sindroma i koronarne bolesti nivo cirkulišućeg adiponektina može biti rani marker kardiovaskularnih događaja. Cilj ove studije bio je da se utvrdi povezanost nivoa adiponektina i parametara insulinske rezistencije i gojaznosti kod bolesnika sa metaboličkim sindromom i/ili koronarnom bolešću, kao i da se proceni prediktivni značaj nivoa adiponektina kao biomarkera ovih entiteta. **Metode.** Studija je uključila 100 bolesnika sa metaboličkim sindromom i/ili koronarnom bolešću različitog stepena insulinske rezistencije i zdrave ispitanike sa normalnom glikoregulacijom. Nivo serumskog adiponektina, glukoze našte, insulinemije našte, HOMA-IR indeksa i antropometrijski parametri određivani su kod

svih ispitanika. Adiponektin je meren korišćenjem ultrasenzitivnog ELISA metoda. Insulinemija je određivana radioimunoesej (RIA) metodom. Prisustvo glikemijskih poremećaja procenjeno je na osnovu testa oralne glukozne tolerancije (OGTT). **Rezultati.** Nivo adiponektina bio je u inverznoj korelaciji sa starošću i parametrima insulinske rezistencije i gojaznosti. Snižena nivoa adiponektina bila su udružena sa rastućim stepenom insulinske rezistencije. Najvažnije, statistički značajan pad nivoa adiponektina bio je u stadijumu predijabetesa ($p < 0,01$). Prediktorska vrednost nivoa adiponektina iznosila je $1,356,32 \pm 402,65$ pg/mL. **Zaključak.** Dobijeni rezultati ukazuju na to da adiponektin može biti koristan marker u identifikaciji osoba sa povećanim rizikom od razvoja metaboličkog sindroma i koronarne bolesti, kao i prediktor predijabetesa.

Ključne reči:
adiponektin; biološki pokazatelji; metabolički sindrom x;
koronarna bolest.

Introduction

Dysfunctional adipose tissue links obesity to cardiovascular disease by secreting a multitude of bioactive adipokines with detrimental effects on the cardiovascular system. However, adipocytes secrete a unique vasculoprotective adipokine – adiponectin^{1,2}.

Adiponectin is a hormone secreted primarily from the mature adipocytes and circulates at a concentration significantly higher in metabolically healthy individuals of normal body weight. Recent studies have shown that the levels of adiponectin are in a statistically more significant inverse correlation with visceral than with total adipose tissue, indicating that the concentration of serum adiponectin is not determined only by the amount of adipose tissue, but also by its distribution^{3,4}.

Interestingly, the part of the human adiponectin chromosome 3 (3q27) contains the “quantitative trait locus” (QTL) with a strong influence on the phenotypes of hypertension, prediabetes and metabolic syndrome^{5,6}.

In physiological conditions, adiponectin has a protective role in the maintenance of insulin sensitivity, anti-inflammatory role in the prevention of pro-inflammatory response to numerous cytokines, vasculoprotective role in the maintenance of the vasculature in vasodilating condition and inhibition of proliferation of smooth muscle cells of blood vessels. Adiponectin realizes the primary effect of insulin sensitizer in the skeletal muscles and the liver, through inhibition of lipid synthesis and glyconeogenesis, maintaining glucose, triglycerides and free fatty acids in blood by means of adiponectin receptor AdipoR and molecules AMPK, PPAR- α and other unknown signaling pathways⁷⁻⁹. Since hypo-adiponectinaemia contributes to the pathophysiology of the metabolic syndrome (MS) and coronary artery disease, the level of circulating adiponectin may be an early marker of cardiovascular events.

In recent years, adiponectin as hormone has attracted the attention of many researchers due to its characteristics, it is easy to measure, stable in the circulation, and its circulatory concentrations inversely correlated with other potential cardiovascular markers such as other adipokines (leptin and resistin) and lipids.

Method

This cross-sectional study included 100 patients with metabolic syndrome and/or coronary artery disease with different degree of insulin resistance (IR) and healthy, normo-glycemic individuals (50 men and 50 women), aged 40–75 years. Blood for venous blood samples (10 mL), collected from all individuals, after an overnight 12 hour fast, was drawn from the antecubital vein between 8.30 and 9.30 *am*. Serum was separated and then quickly stored at -70°C for biochemical analyses. Determination of the concentration of hormone adiponectin was done at the Center for Molecular Medicine of Stem Cell, Faculty of Medical Sciences, University of Kragujevac.

The criteria for non-inclusion were: patients with associated diseases of the digestive and renal systems (malabsorption syndrome, liver and renal insufficiency), acute infecti-

ons in the past three months, neoplastic diseases, diabetes mellitus.

All examinees were measured for anthropometric characteristics: body mass (kg), body height (cm), body mass index (BMI) as the ratio of body mass and the height square (kg/m²), waist circumference (cm), hip circumference (cm), waist/hip ratio (WHR), and body fat percentage (FAT %).

Determination of the total quantity of adipose tissue (Whole body fat/DEXA) was performed on the DXA (dual energy X-ray absorptiometry scan) device Densitometer Hologic Dycscovery and shown in percentage (%); obesity was defined according to the following values: up to 40 years for men > 22% and women > 35%, over 40 years for men > 25% and women > 38%¹⁰.

Insulinemia was determined in the Laboratory for Radioactive Isotopes, at the Department of Nuclear Medicine, Clinical Center “Kragujevac”, using the diagnostic kit radioimmunoassay – RIA INSULIN (CIS). The reference range for insulin was 4.3 mU/L to 19.9 mU/L and intra- and interassay coefficients of variation were 4.5% and 5.0 %.

Based on the oral glucose tolerance test (OGTT), assessment of the existence of glycemic disorders was performed. Glycoregulation disorders were determined according to the current WHO classification¹¹.

Determination of the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index as a parameter of insulin resistance and HOMA- β index as an indicator of the function of pancreatic β -cells were determined according to homeostasis model assessment formula¹². There are no standardized reference values for the HOMA-IR index due to conflicting values of different ethnic groups¹³. Therefore, based on the obtained values HOMA-IR index, the patients were grouped in the terciles. The highest tercile of the obtained values have 27% higher risk of developing a cardiovascular event than those in the lowest tercile of the insulin resistance.

The adiponectin concentration in serum was determined by commercial ELISA (Enzyme-linked immunosorbent assay) kit specific for human adiponectin (Human Adiponectin Duo Set ELISA Development kit, R & D systems, USA)¹⁴. Based on the measured values of the standards, a standard curve was created, and then the values for each individual sample were calculated. All samples were measured in triplicate. The measuring range of the method was 62.5–4000 pg/mL and intra- and interassay coefficients of variation were 4.5% and 5.0%.

For more detailed analysis of the correlation between adiponectin level and insulin resistance in accordance with the natural course of MS and IR stages and for determination of the adiponectin levels in IR stages, depending on glucose tolerance and values of blood insulin, the patients were divided into four groups: group 1 – normal glucose tolerance and normoinsulinemia; group 2 – normal glucose tolerance and hyperinsulinemia; group 3 – pathological glucose tolerance and hyperinsulinemia; group 4 – pathological glucose tolerance and normoinsulinemia and/or hyperinsulinemia.

Data regarding coronary artery diseases were taken under coronarographic findings from the patients’ medical records. Significant coronary artery stenosis was defined as >

50% reduction of absolute lumen diameter of major epicardial arteries or their major branches.

Statistical analysis was performed using descriptive and analytical methods. The mean values of the parameters are shown as the arithmetic mean (x) ± standard deviation (SD). The differences in the mean values of adiponectin levels and parameters of metabolic syndrome and coronary artery disease among groups were determined by variance analysis (ANOVA), while the correlation of adiponectin levels with these parameters was determined using multiple regression analysis and Pearson's (r) and Spearman's correlation coefficient (ρ).

All statistical analyzes were performed for the statistical significance level of $p < 0.05$.

Results

This study included 50 men and 50 women, average age 53.19 ± 15.0 years.

The results showed that adiponectin level inversely correlated with age ($\rho = -0.015$; $p > 0.05$) and was significantly higher in the female patients ($r = 0.208$; $p < 0.05$).

The adiponectin levels showed a negative correlation with obesity parameters ($R = 0.437$, $p < 0.001$); the most significant impact on the adiponectin level had waist circumference (Figure 1) and waist/hip ratio WHR ($r = -0.203$; $p < 0.05$), while BMI ($r = -0.138$) and FAT(%) ($r = -0.020$) did not have a significant impact on the level of adiponectin.

A correlation between the adiponectin level and parameters of IR [fasting glycemia (OGTT I), glycemia in the 120th minute (OGTT II), insulin, HOMA-IR and HOMA-β] was found in the whole study group, using the Pearson's correlation coefficient (Table 1). The results showed a negative, relatively weak correlation, but highly significant ($p < 0.01$) with OGTT I ($r = -0.292$) and HOMA-IR ($r = -0.259$), and a significant correlation with insulin ($r = -0.238$, $p < 0.05$), and in the second part of Table a significant and relatively strong correlation between the IR parameters.

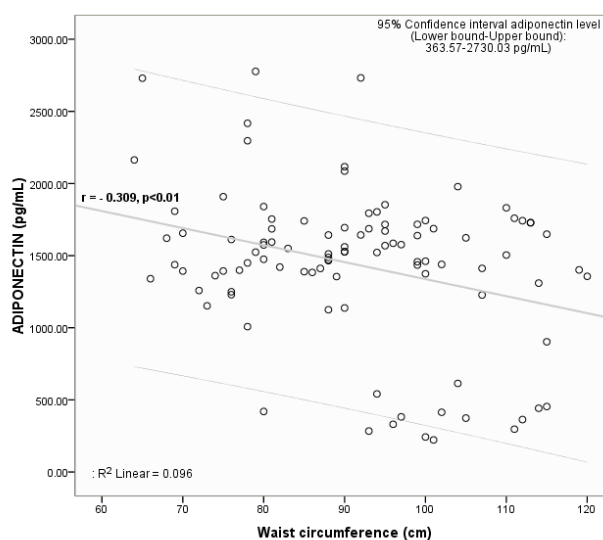


Fig. 1 – Relationship between adiponectin level and waist circumference.

A correlation between the adiponectin level and IR parameters, their relationships and a significance in the prognostic set, using multiple regression analysis are shown in Table 2.

A correlation between the adiponectin level and IR parameters was moderate and significant ($R = 0.374$, $p < 0.01$). In the prognostic set of IR parameters in the model, the most significant impact on the level of adiponectin ($p < 0.05$) had OGTT I ($\beta = -0.312$) and insulin ($\beta = -0.211$). Pearson and partial correlation coefficients are shown in the Correlations column.

The one-way analysis of variance was used to determine whether there were any significant differences between adiponectin levels in the groups of patients with the different IR stages. There was a statistically significant difference between adiponectin levels between the first and the second groups ($p < 0.01$). There was no statistically significant difference between the other groups of patients. Comparing to the stage of normal glucose regulation, in the first stage of “pre-

Table 1
Correlation (Pearson's coefficient) between adiponectin level and parameters of insulin resistance

Parameters	Adiponectin	OGTT I	OGTT II	Insulin	INDEX	
					HOMA-IR	HOMA-β
OGTT I	- 0.292**	-	-	-	-	-
OGTT II	- 0.069	0.595***	-	-	-	-
Insulin	- 0.238*	0.353***	0.242*	-	-	-
HOMA-IR	- 0.259**	0.526***	0.342**	0.970***	-	-
HOMA-β	- 0.062	- 0.068	- 0.023	0.585***	0.480***	-

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; OGTT – oral glucose tolerance test; HOMA-IR – homeostasis model assessment of insulin resistance.

Table 2

Correlation between the adiponectin level and parameters of insulin resistance

MODEL	R	R ² Square change	Sig.	Predictors	Unstandar. coefficient B	Standard. coefficient	Sig.	Correlations	
								Zero-order	Part
Adipo-nectin (Backward)	0.374**	0.140	0.002	(constant)	2536.065		.000		
				OGTT I	- 137.731	- 0.312*	.013	- 0.292**	- 0.239
				OGTT II	- 37.177	- 0.174	.144	- 0.069	- 0.139
				Insulin	- 175.899	- 0.211*	.044	- 0.238*	- 0.193

* $p < 0.05$; ** $p < 0.01$; OGTT – oral glucose tolerance test.

diabetes”, a condition of normal glucose tolerance and hiperinsulinemia (Figure 2), showed an increase in insulin and a sudden decrease in adiponectin level. In the second stage, the impaired glucose tolerance, hyperglycemia was maintained, while glycemia in the 120th min continuously increased, continued in the final stage of insulin resistance, also with fasting glycemia, which was constantly increasing, until the end of this stage maintained hyperglycemia at a high level. The levels of adiponectin, after a sharp decrease in the first stage of increased fasting glycemia, rapidly increased in the second stage, as induced response to an increase in glycemia and the impaired glucose tolerance, and in the final stage of insulin resistance it continued increasing and maintained the achieved level, significantly below the initial values, in terms of high hyperglycemia and insulin resistance.

A correlation between adiponectin levels and parameters of insulin resistance was negative. In the normal weight patients there was a significant correlation ($p < 0.01$) with insulin ($r = -0.287$) and HOMA-IR index ($r = -0.299$), and less significant with the OGTT I ($r = -0.266$, $p < 0.05$), while in the obese patients there was no significant correlation.

In view of the importance of cardiovascular risk in metabolic syndrome, the incidence of coronary artery disease was determined in different phases of its development. In the stages during metabolic syndrome when metabolic decompensation is manifested, and the appearance of condition of normal glucose tolerance and hiperinsulinemia, relative incidence of coronary artery disease increases compared to the initial condition. In the first group 30% of patients had coronary artery disease, in the second one 36%, in the third one 24%, and in the fourth one 12%.

Discussion

With the emergence of obesity and development of MS, the process of deregulation of adipocytes leads to of intracel-

lular function disorders, and the results are insulin resistance at the level of adipose tissue, increased production of adipokines, free fatty acids, and other inflammatory mediators in the form of insulin resistance, particularly in skeletal muscles and liver. Insulin resistance further affects the cells of vascular membrane, which further increases the risk of cardiovascular diseases¹⁵.

Over the last decade through many clinical studies^{16,17}, as well as this one, reported that the level of adiponectin paradoxically decreases in the states of MS, MS-associated diseases and coronary artery diseases (CAD), as well as in acute phases of CAD¹⁸, as a reaction to an abnormal inflammatory response. Due to the inhibitory impact of adiponectin on the production of TNF- α and other proinflammatory cytokines, the expression of adhesion molecules, and the growth-factor-induced proliferation of smooth muscle cells, are significant mostly in the early stages of atherosclerosis and acute exacerbations. The protective effects of adiponectin are often associated with a proven reduction of inflammation and endothelial dysfunction, which are in the basis of MS and CAD occurrence, which leads to the conclusion that hypoadiponectinaemia, haemodynamic vascular abnormalities, as well as the complications of atherosclerosis are consequently correlated.

The results of this study, as well as the study of Wang et al.¹⁹ show that in middle-aged patients serum levels of adiponectin in relation to gender, are more significant in men with CAD, whereas in women they are more significant in the group with MS and prediabetes, which explains that there is male predisposition towards the development of coronary artery disease, whereas in women towards metabolic disorders, due to the up-regulation of estrogen to adiponectin in premenopausal women. Adiponectin level in men is significantly lower than in women due to the inhibitory effects of testosterone on its production.

The results of recent studies^{16,20}, and the results of this research show that the patients with CAD and MS have the

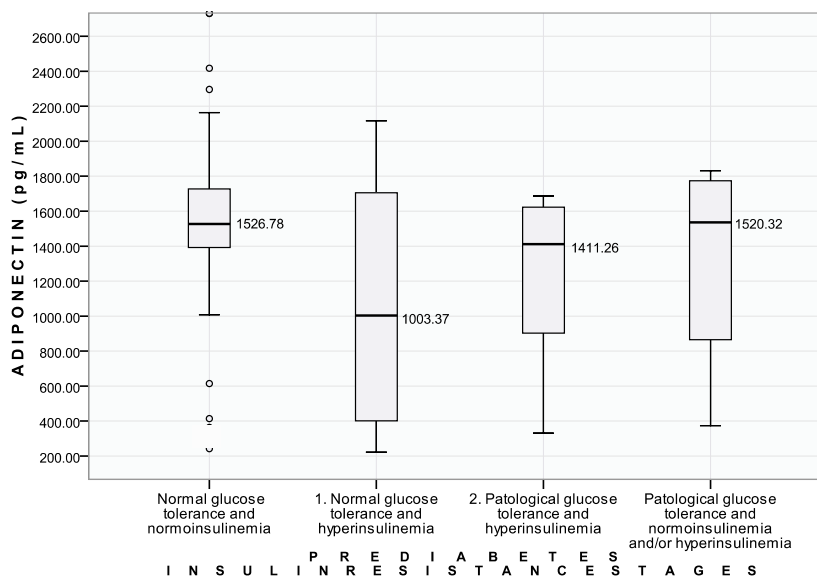


Fig. 2 – Adiponectin serum level according to insulin resistance.

lowest levels of adiponectin, higher in the patients with MS than in the patients with CAD; the highest level of adiponectin is in healthy examinees, and women have higher levels of adiponectin than men. The reason for significantly lower serum levels of adiponectin in patients with MS and CAD should not be looked for in the combined pathogenesis of the diseases, but in common genetic predisposition by mediation of transcription factors (PPAR- γ , FOKS), which with the external risk factors leads to the expression of both conditions²⁰.

Although MS and atherosclerosis in MS include lower levels of inflammation in their pathogenesis, their molecular pathogenetic mechanisms are different. Clinically manifested MS immediately results in a decrease of adiponectin levels, since it is in the stage of adiponectin decompensation, when endothelial cells do not have enough signals for the secretion of adiponectin from adipose tissue. Probably the early stage of MS, or just prior to MS, is accompanied by increasing levels of adiponectin in a so-called compensation phase, while later results in a sharp decrease, when the levels of adiponectin signalling are worn out. During the formation of atherosclerotic plaques, macrophages, not yet converted into the foamy cells secrete pro-inflammatory cytokines leading to the inhibitory impact on the expression of adiponectin and destabilisation of atherosclerotic plaque. In a stable form of multiple coronary artery disease, where the adiponectin levels are slightly increased, the state of the mild adiponectin resistance is maintained, as opposed to the sudden decrease in the adiponectin level created in the acute coronary syndrome.

The results show that the level of adiponectin significantly decreases with the increase of nutrition/obesity level, especially visceral adipose tissue, as evidenced by recently published studies^{21,22}, while the total amount of adipose tissue does not show any significant effect.

Among the obesity parameters waist circumference is the most significant showing strongest correlation with the level of adiponectin, thus confirming the clinical significance of its measurements.

It is important to note that large adipocytes, which are particularly contained in visceral adipose tissue, create less anti-inflammatory adiponectin, and more proinflammatory cytokines and adipokines, supporting vicious cycle of low level chronic inflammation²³.

Persons with normal weight, but increased amount of visceral adipose tissue, have an increased risk of developing MS and CAD. On the other hand, obese, but metabolically healthy persons may have an increased insulin sensitivity, and thus the protecting effect of metabolic diseases associated with obesity over combined and partly crossed adiponectin-insulin signaling pathways²⁴.

Inverse association of adiponectin level with parameters of insulin resistance is confirmed by many studies^{25,26}, of

which the Shams et al.²⁵ study, with similar study sample by gender and age, in patients with CAD, shows a significant negative correlation ($p < 0.01$) with insulin level ($r = - 0.192$) and HOMA-index ($r = - 0.216$), and Mohan's study²⁷ a significant negative correlation of adiponectin level with fasting glucose and HOMA-IR index ($p < 0.001$).

In terms of hypoadiponectinaemia, MS, and chronic inflammation, it comes to signalization disorders in insulin and adiponectin ways and their receptors, and subsequent formation of insulin resistance. Disorders in adiponectin and insulin signalization lead to the occurrence of metabolic and vascular disorders, including endothelial dysfunction and metabolic syndrome.

The precise correlation of hypoadiponectinaemia and damaged signalization on insulin signalling pathway is not fully understood. However, there are several mechanisms of negative correlation between adiponectin level and parameters of insulin resistance: damaged signalization under the influence of TNF- α , disorder of the constituent components of insulin receptors, disordered function of APPL protein, down-regulation of genes PPAR- γ and PPAR- α and decreased expression of adiponectin receptor (AdipoR), as well as the disorder of all the other signalling molecules (AMPK, Akt, PKB, p38 MAPK) and the secondary messengers of insulin/adiponectin cascade pathways at the transcriptional and postranslational level⁷⁻⁹.

Regardless of the cause of prediabetic state, it appears that changes in adiponectin level may validly reflect on the severity and stage of the IR evolution, as demonstrated by the results of this study, as well as by the results of other ones obtained in prediabetic patients²⁸, wherein the statistical significance was higher compared to non-diabetic patients.

Bearing in mind the aforementioned, adiponectin could be a representative marker of the early stages of insulin resistance, even in chronic cardiovascular damage. However, there are still too small number of studies dealing with the relationship of adiponectin level and insulin sensitivity in pre-diabetes, in order to determine the extent of change in adiponectin level as a routine clinical biomarker.

Conclusion

It can be emphasized that this study supports the hypothesis that adiponectin plays the central role in maintaining the functioning of adipose tissue, insulin sensitivity and energy consumption of the body.

Bearing in mind that the serum concentration of this significant hormone reflects early changes in the development of insulin resistance and prediabetes leading to the progression and acceleration of the creation of atherosclerotic lesions, adiponectin might be a significant and independent clinical marker of metabolic syndrome and coronary artery disease.

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